

SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials

An-Wen Chan, MD, DPhil; Jennifer M. Tetzlaff, MSc; Douglas G. Altman, DSc; Andreas Laupacis, MD; Peter C. Gøtzsche, MD, DrMedSci; Karmela Krleža-Jerić, MD, DSc; Asbjørn Hróbjartsson, PhD; Howard Mann, MD; Kay Dickersin, PhD; Jesse A. Berlin, ScD; Caroline J. Doré, BSc; Wendy R. Parulekar, MD; William S.M. Summerskill, MBBS; Trish Groves, MBBS; Kenneth F. Schulz, PhD; Harold C. Sox, MD; Frank W. Rockhold, PhD; Drummond Rennie, MD; and David Moher, PhD

The protocol of a clinical trial serves as the foundation for study planning, conduct, reporting, and appraisal. However, trial protocols and existing protocol guidelines vary greatly in content and quality. This article describes the systematic development and scope of SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013, a guideline for the minimum content of a clinical trial protocol.

The 33-item SPIRIT checklist applies to protocols for all clinical trials and focuses on content rather than format. The checklist recommends a full description of what is planned; it does not prescribe how to design or conduct a trial. By providing guidance

for key content, the SPIRIT recommendations aim to facilitate the drafting of high-quality protocols. Adherence to SPIRIT would also enhance the transparency and completeness of trial protocols for the benefit of investigators, trial participants, patients, sponsors, funders, research ethics committees or institutional review boards, peer reviewers, journals, trial registries, policymakers, regulators, and other key stakeholders.

Ann Intern Med. 2013;158:200-207.

For author affiliations, see end of text.

This article was published at www.annals.org on 8 January 2013.

www.annals.org

The protocol of a clinical trial plays a key role in study planning, conduct, interpretation, oversight, and external review by detailing the plans from ethics approval to dissemination of results. A well-written protocol facilitates an appropriate assessment of scientific, ethical, and safety issues before a trial begins; consistency and rigor of trial conduct; and full appraisal of the conduct and results after trial completion. The importance of protocols has been emphasized by journal editors (1–6), peer reviewers (7–10), researchers (11–15), and public advocates (16).

Despite the central role of protocols, a systematic review revealed that existing guidelines for protocol content vary greatly in their scope and recommendations, seldom describe how the guidelines were developed, and rarely cite broad stakeholder involvement or empirical evidence to support their recommendations (17). These limitations may partly explain why an opportunity exists to improve the quality of protocols. Many protocols for randomized trials do not adequately describe the primary outcomes (inadequate for 25% of trials) (18, 19), treatment allocation methods (inadequate for 54% to 79%) (20, 21), use of blinding (inadequate for 9% to 34%) (21, 22), methods for reporting adverse events (inadequate for 41%) (23), components of sample size calculations (inadequate for 4% to 40%) (21, 24), data analysis plans (inadequate for 20% to 77%) (21, 24–26), publication policies (inadequate for 7%) (27), and roles of sponsors and investigators in study design or data access (inadequate for 89% to 100%) (28, 29). The problems that underlie these protocol deficiencies may in turn lead to avoidable protocol amendments, poor trial conduct, and inadequate reporting in trial publications (15, 30).

In response to these gaps in protocol content and guidance, we launched the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) initia-

tive in 2007. This international project aims to improve the completeness of trial protocols by producing evidence-based recommendations for a minimum set of items to be addressed in protocols. The SPIRIT 2013 Statement includes a 33-item checklist (Table 1) and diagram (Figure). An associated explanatory paper (SPIRIT 2013 Explanation and Elaboration) (31) details the rationale and supporting evidence for each checklist item, along with guidance and model examples from actual protocols.

DEVELOPMENT OF THE SPIRIT 2013 STATEMENT

The SPIRIT 2013 Statement was developed in broad consultation with 115 key stakeholders, including trial investigators ($n = 30$); health care professionals ($n = 31$); methodologists ($n = 34$); statisticians ($n = 16$); trial coordinators ($n = 14$); journal editors ($n = 15$); and representatives from the research ethics community ($n = 17$), industry and nonindustry funders ($n = 7$), and regulatory agencies ($n = 3$), whose roles are not mutually exclusive. As detailed later, the SPIRIT guideline was developed through 2 systematic reviews, a formal Delphi consensus process, 2 face-to-face consensus meetings, and pilot-testing (32).

The SPIRIT checklist evolved through several iterations. The process began with a preliminary checklist of 59 items derived from a systematic review of existing protocol guidelines (17). In 2007, 96 expert panelists from 17 low- ($n = 1$), middle- ($n = 6$), and high-income ($n = 10$) countries refined this initial checklist over 3 iterative Delphi consensus survey rounds by e-mail (33). Panelists rated each item on a scale of 1 (not important) to 10 (very important), suggested new items, and provided comments that were circulated in subsequent rounds. Items with a median score of 8 or higher in the final round were included, whereas those rated 5 or lower were excluded.

Table 1. SPIRIT 2013 Checklist: Recommended Items to Address in a Clinical Trial Protocol and Related Documents*

Section/Item	Item Number	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry.
	2b	All items from the World Health Organization Trial Registration Data Set (Appendix Table , available at www.annals.org)
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for DMC)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)
Methods		
Participants, interventions, and outcomes		
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (Figure).
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size
Assignment of interventions (for controlled trials)		
Allocation		
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions.
	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Allocation concealment mechanism	16b	
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Continued on following page

Table 1—Continued

Section/Item	Item Number	Description
Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol.
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)
Monitoring		
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking REC/IRB approval
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

DMC = data monitoring committee; IRB = institutional review board; REC = research ethics committee; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.

* It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation and Elaboration (31) for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group and is reproduced with permission.

Items rated between 5 and 8 were retained for further discussion at the consensus meetings.

After the Delphi survey, 16 members of the SPIRIT Group (named as authors of this paper) met in December 2007 in Ottawa, Ontario, Canada, and 14 members met in September 2009 in Toronto, Ontario, Canada, to review the survey results, discuss controversial items, and refine

the draft checklist. After each meeting, the revised checklist was recirculated to the SPIRIT Group for additional feedback.

A second systematic review identified empirical evidence about the relevance of specific protocol items to trial conduct or risk of bias. The results of this review informed the decision to include or exclude items on the SPIRIT

checklist. This review also provided the evidence base of studies cited in the SPIRIT 2013 Explanation and Elaboration paper (31). Some items had little or no identified empirical evidence (for example, the title) and are included in the checklist on the basis of a strong pragmatic or ethical rationale.

Finally, we pilot-tested the draft checklist in 2010 and 2011 with University of Toronto graduate students who used the document to develop trial protocols as part of a master's-level course on clinical trial methods. Their feedback on the content, format, and usefulness of the checklist was obtained through an anonymous survey and incorporated into the final SPIRIT checklist.

DEFINITION OF A CLINICAL TRIAL PROTOCOL

Although every study requires a protocol, the precise definition of a protocol varies among individual investigators, sponsors, and other stakeholders. For the SPIRIT initiative, the protocol is defined as a document that provides sufficient detail to enable understanding of the background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans, and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigor from ethics approval to dissemination of results.

The protocol is more than a list of items. It should be a cohesive document that provides appropriate context and narrative to fully understand the elements of the trial. For example, the description of a complex intervention may need to include training materials and figures to enable replication by persons with appropriate expertise.

The full protocol must be submitted for approval by an institutional review board (IRB) or research ethics committee (34). It is recommended that trial investigators or sponsors address the SPIRIT checklist items in the protocol before submission. If the details for certain items have not yet been finalized, then this should be stated in the protocol and the items updated as they evolve.

The protocol is a "living" document that is often modified during the trial. A transparent audit trail with dates of important changes in trial design and conduct is an essential part of the scientific record. Trial investigators and sponsors are expected to adhere to the protocol as approved by the IRB and to document amendments made in the most recent protocol version. Important protocol amendments should be reported to IRBs and trial registries as they occur and subsequently be described in trial reports.

SCOPE OF THE SPIRIT 2013 STATEMENT

The SPIRIT 2013 Statement applies to the content of a clinical trial protocol, including its appendices. A clinical trial is a prospective study in which 1 or more interventions are assigned to human participants to assess the effects on health-related outcomes. The primary scope of

Figure. Example template of recommended content for the schedule of enrollment, interventions, and assessments.

	Study Period								
	Enrollment	Allocation	Postallocation						Closeout
Time point*	-t ₁	0	t ₁	t ₂	t ₃	t ₄	etc.		t _x
Enrollment:									
Eligibility screen	X								
Informed consent	X								
[List other procedures]	X								
Allocation		X							
Interventions:									
[Intervention A]			◆	—	◆				
[Intervention B]			X		X				
[List other study groups]			◆	—	◆				
Assessments:									
[List baseline variables]	X	X							
[List outcome variables]				X		X	etc.		X
[List other data variables]			X	X	X	X	etc.		X

Recommended content can be displayed using various schematic formats. See SPIRIT 2013 Explanation and Elaboration (31) for examples. This template is copyrighted by the SPIRIT Group and is reproduced with permission. SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.

* List specific time points in this row.

SPIRIT 2013 relates to randomized trials, but the same considerations substantially apply to all types of clinical trials, regardless of study design, intervention, or topic.

The SPIRIT 2013 Statement provides guidance for minimum protocol content. Certain circumstances may warrant additional protocol items. For example, a factorial study design may require specific justification; crossover trials have unique statistical considerations, such as carry-over effects; and industry-sponsored trials may have additional regulatory requirements.

The protocol and its appendices are often the sole repository of detailed information relevant to every SPIRIT checklist item. Using existing trial protocols, we have been able to identify model examples of every item (31), which illustrates the feasibility of addressing all checklist items in a single protocol document. For some trials, relevant details may appear in related documents, such as statistical analysis plans, case record forms, operations manuals, or investigator contracts (35, 36). In these instances, the protocol should outline the key principles and refer to the separate documents so that their existence is known.

The SPIRIT 2013 Statement primarily relates to the content of the protocol rather than its format, which is often subject to local regulations, traditions, or standard operating procedures. Nevertheless, adherence to certain formatting conventions, such as a table of contents; section headings; glossary; list of abbreviations; list of references; and a schematic schedule of enrollment, interventions, and assessments, will facilitate protocol review (**Figure**).

Finally, the intent of SPIRIT 2013 is to promote transparency and a full description of what is planned—not to prescribe how a trial should be designed or conducted. The checklist should not be used to judge trial quality, because the protocol of a poorly designed trial may address all checklist items by fully describing its inadequate design features. Nevertheless, the use of SPIRIT 2013 may improve the validity and success of trials by reminding investigators about important issues to consider during the planning stages.

RELATION TO EXISTING CLINICAL TRIAL GUIDANCE

With its systematic development process, consultation with international stakeholders, and explanatory paper citing relevant empirical evidence (31), SPIRIT 2013 builds on other international guidance applicable to clinical trial protocols. It adheres to the ethical principles mandated by the 2008 Declaration of Helsinki, particularly the requirement that the protocol address specific ethical considerations, such as competing interests (34).

In addition, SPIRIT 2013 encompasses the protocol items recommended by the International Conference on Harmonisation Good Clinical Practice E6 guidance, written in 1996 for clinical trials whose data are intended for submission to regulatory authorities (37). The SPIRIT Statement builds on the Good Clinical Practice guidance by providing additional recommendations on specific key protocol items (for example, allocation concealment, trial registration, and consent processes). In contrast to SPIRIT, the Good Clinical Practice guidance used informal consensus methods, has unclear contributorship, and lacks citation of supporting empirical evidence (38).

The SPIRIT 2013 Statement also supports trial registration requirements from the World Health Organization (39), the International Committee of Medical Journal Editors (40), legislation pertaining to ClinicalTrials.gov (41),

the European Commission (42), and others. For example, item 2b of the SPIRIT checklist recommends that the protocol list the World Health Organization Trial Registration Data Set (**Appendix Table**, available at www.annals.org), which is the minimum amount of information that the International Committee of Medical Journal Editors mandates for trial registries. Having this data set in its own protocol section is intended not only to serve as a form of trial summary but also to help improve the quality of information in registry entries. Registration-specific data could be easily identified in the protocol section and copied into the registry fields. In addition, protocol amendments applicable to this section could prompt investigators to update their registry data.

The SPIRIT 2013 Statement mirrors applicable items from CONSORT 2010 (Consolidated Standards of Reporting Trials) (43). Consistent wording and structure used for items common to both checklists will facilitate the transition from a SPIRIT-based protocol to a final report based on CONSORT. The SPIRIT Group has also engaged leaders of other initiatives relevant to protocol standards, such as trial registries, the Clinical Data Interchange Standards Consortium Protocol Representation Group, and Pragmatic Randomized Controlled Trials in Health-Care, to align international efforts in promoting transparency and high-quality protocol content.

POTENTIAL EFFECT

An extensive range of stakeholders could benefit from widespread use of the SPIRIT 2013 Statement and its explanatory paper (**Table 2**). Pilot-testing and informal feedback have shown that it is particularly valuable for trial investigators when they draft their protocols. It can also serve as an informational resource for new investigators, peer reviewers, and IRB members.

There is also potential benefit for trial implementation. The excessive delay from the time of protocol development to ethics approval and the start of participant recruitment remains a major concern for clinical trials (44). Improved completeness of protocols could help increase the efficiency of protocol review by reducing avoidable queries to investigators about incomplete or unclear information. With full documentation of key information and increased awareness of important considerations before the trial begins, the use of SPIRIT may also help to reduce the number and burden of subsequent protocol amendments—many of which can be avoided with careful protocol drafting and development (15). Widespread adoption of SPIRIT 2013 as a single standard by IRBs, funding agencies, regulatory agencies, and journals could simplify the work of trial investigators and sponsors, who could fulfill the common application requirements of multiple stakeholders with a single SPIRIT-based protocol. Better protocols would also help trial personnel to implement the study as the protocol authors intended.

Table 2. Potential Benefits and Proposed Stakeholder Actions for Supporting Adherence to SPIRIT 2013

Stakeholder	Proposed Actions	Potential Benefits
Clinical trial groups, investigators, sponsors	Adopt SPIRIT as standard guidance Use as tool for writing protocols	Improved quality, completeness, and consistency of protocol content Enhanced understanding of rationale and issues to consider for key protocol items Increased efficiency of protocol review
Research ethics committees/institutional review boards, funding agencies, regulatory agencies	Mandate or encourage adherence to SPIRIT for submitted protocols Use as training tool	Improved quality, completeness, and consistency of protocol submissions Increased efficiency of review and reduction in queries about protocol requirements
Educators	Use SPIRIT checklist and explanatory paper as a training tool	Enhanced understanding of the rationale and issues to consider for key protocol items
Patients, trial participants, policymakers	Advocate use of SPIRIT by trial investigators and sponsors	Improved protocol content relevant to transparency, accountability, critical appraisal, and oversight
Trial registries	Encourage SPIRIT-based protocols Register full protocols to accompany results disclosure	Improved quality of registry records Prompt for trialists to update registry record when SPIRIT checklist item 2b (Registration Data Set) is updated Improved quality, completeness, and consistency of protocol content for registries that house full protocols and results
Journal editors and publishers	Endorse SPIRIT as standard guidance for published and unpublished protocols Include reference to SPIRIT in instructions for authors Ask that protocols be submitted with manuscripts, circulate them to peer reviewers, and encourage authors to make them available as Web appendices	Improved quality, completeness, and consistency of protocol content Enhanced peer review of trial manuscripts through improved protocol content, which can be used to assess protocol adherence and selective reporting Improved transparency and interpretation of trials by readers

SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.

Furthermore, adherence to SPIRIT 2013 could help ensure that protocols contain the requisite information for critical appraisal and trial interpretation. High-quality protocols can provide important information about trial methods and conduct that is not available from journals or trial registries (45–47). As a transparent record of the researchers' original intent, comparisons of protocols with final trial reports can help to identify selective reporting of results and undisclosed amendments (48), such as changes to primary outcomes (19, 49). However, clinical trial protocols are not generally accessible to the public (45). The SPIRIT 2013 Statement will have a greater effect when protocols are publicly available to facilitate full evaluation of trial validity and applicability (11, 12, 14, 50).

The SPIRIT 2013 guideline needs the support of key stakeholders to achieve its greatest impact (Table 2), as seen with widely adopted reporting guidelines, such as CONSORT (51). We will post the names of organizations that have endorsed SPIRIT 2013 on the SPIRIT Web site (www.spirit-statement.org) and provide resources to facilitate implementation. Widespread adoption of the SPIRIT recommendations can help improve protocol drafting, content, and implementation; facilitate registration, efficiency, and appraisal of trials; and ultimately enhance transparency for the benefit of patient care.

From Women's College Research Institute, Women's College Hospital, and Keenan Research Centre at the Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; Ottawa Methods Centre, Ottawa Hospital Research Institute, Ethics Office, Canadian Institutes of Health Research, and University of Ottawa, Ottawa, Ontario, Canada; Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom; Nordic Cochrane Centre,

Rigshospitalet, Copenhagen, Denmark; University of Utah School of Medicine, Salt Lake City, Utah; Center for Clinical Trials, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Janssen Research & Development, Janssen Pharmaceutical Companies of Johnson & Johnson, Titusville, New Jersey; UK Medical Research Council Clinical Trials Unit, *The Lancet*, and *BMJ*, London, United Kingdom; NCIC Clinical Trials Group, Cancer Research Institute, Queen's University, Kingston, Ontario, Canada; Quantitative Sciences, FHI 360, and GlaxoSmithKline, Research Triangle Park, North Carolina; The Dartmouth Institute for Health Policy and Clinical Practice, The Geisel School of Medicine at Dartmouth, Hanover, New Hampshire; The PR Lee Institute for Health Policy Studies, University of California, San Francisco, San Francisco, California.

Disclaimer: Dr. Krlęza-Jerić was formerly employed by the Canadian Institutes of Health Research (Knowledge Translation Branch), and Dr. Parulekar is affiliated with the NCIC Clinical Trials Group. The funders otherwise had no input into the design and conduct of the project; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Berlin is employed by the Janssen Pharmaceutical Companies of Johnson & Johnson, Dr. Sox is Editor Emeritus of *Annals of Internal Medicine*, and Dr. Rockhold is employed by GlaxoSmithKline.

Acknowledgment: The authors thank Drs. Mona Loufty and Patricia Parkin for pilot-testing the SPIRIT checklist with their graduate course students. The authors also acknowledge the participation of Dr. Genevieve Dubois-Flynn in the 2009 SPIRIT meeting.

Grant Support: Financial support for the SPIRIT meetings was provided by the Canadian Institutes of Health Research (grant DET-106068), National Cancer Institute of Canada (now Canadian Cancer Society Research Institute), and Canadian Agency for Drugs and Technologies in Health. The Canadian Institutes of Health Research has also funded ongoing dissemination activities (grant MET-117434).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-1905.

Requests for Single Reprints: An-Wen Chan, MD, DPhil, Women's College Research Institute, Women's College Hospital, University of Toronto, 790 Bay Street, Toronto, Ontario M5G 1N8, Canada; e-mail, anwen.chan@utoronto.ca.

Current author addresses and author contributions are available at www.annals.org.

References

- Rennie D. Trial registration: a great idea switches from ignored to irresistible. *JAMA*. 2004;292:1359-62. [PMID: 15355937]
- Strengthening the credibility of clinical research [Editorial]. *Lancet*. 2010;375:1225. [PMID: 20382309]
- Summerskill W, Collingridge D, Frankish H. Protocols, probity, and publication. *Lancet*. 2009;373:992. [PMID: 19304003]
- Jones G, Abbasi K. Trial protocols at the BMJ [Editorial]. *BMJ*. 2004;329:1360. [PMID: 15591544]
- Groves T. Let SPIRIT take you . . . towards much clearer trial protocols. *BMJ Group Blogs*. 25 September 2009. Accessed at <http://blogs.bmj.com/bmj/2009/09/25/trish-groves-let-spirit-take-you-towards-much-clearer-trial-protocols/> on 1 October 2012.
- Altman DG, Furberg CD, Grimshaw JM, Rothwell PM. Lead editorial: trials-using the opportunities of electronic publishing to improve the reporting of randomised trials [Editorial]. *Trials*. 2006;7:6. [PMID: 16556322]
- Turner EH. A taxpayer-funded clinical trials registry and results database [Editorial]. *PLoS Med*. 2004;1:e60. [PMID: 15562322]
- Coults D. Ethical considerations in the interpretation and communication of clinical trial results. *Proc Am Thorac Soc*. 2007;4:194-8. [PMID: 17494731]
- Siegel JP. Editorial review of protocols for clinical trials [Letter]. *N Engl J Med*. 1990;323:1355. [PMID: 2215630]
- Murray GD. Research governance must focus on research training. *BMJ*. 2001;322:1461-2.
- Chan A-W. Access to clinical trial data [Editorial]. *BMJ*. 2011;342:d80. [PMID: 21228020]
- Miller JD. Registering clinical trial results: the next step. *JAMA*. 2010;303:773-4. [PMID: 20179288]
- Krleža-Jerić K, Chan A-W, Dickersin K, Sim I, Grimshaw J, Gluud C. Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa statement (part 1). *BMJ*. 2005;330:956-8. [PMID: 15845980]
- Lassere M, Johnson K. The power of the protocol. *Lancet*. 2002;360:1620-2. [PMID: 12457782]
- Getz KA, Zuckerman R, Cropp AB, Hindle AL, Krauss R, Kaitin KI. Measuring the incidence, causes, and repercussions of protocol amendments. *Drug Inf J*. 2011;45:265-75.
- Public Citizen Health Research Group v. Food and Drug Administration, 964 F Supp. 413 (DDC 1997).
- Tetzlaff JM, Chan A-W, Kitchen J, Sampson M, Tricco A, Moher D. Guidelines for randomized clinical trial protocol content: a systematic review. *Syst Rev*. 2012;1:43. [PMID: 23006870]
- Chan A-W, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA*. 2004;291:2457-65. [PMID: 15161896]
- Smyth RM, Kirkham JJ, Jacoby A, Altman DG, Gamble C, Williamson PR. Frequency and reasons for outcome reporting bias in clinical trials: interviews with trialists. *BMJ*. 2011;342:e7153. [PMID: 21212122]
- Pildal J, Chan A-W, Hróbjartsson A, Forfang E, Altman DG, Gøtzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. *BMJ*. 2005;330:1049. [PMID: 15817527]
- Mhaskar R, Djulbegovic B, Magazín A, Soares HP, Kumar A. Published methodological quality of randomized controlled trials does not reflect the actual quality assessed in protocols. *J Clin Epidemiol*. 2012;65:602-9. [PMID: 22424985]
- Hróbjartsson A, Pildal J, Chan A-W, Haahr MT, Altman DG, Gøtzsche PC. Reporting on blinding in trial protocols and corresponding publications was often inadequate but rarely contradictory. *J Clin Epidemiol*. 2009;62:967-73. [PMID: 19635403]
- Scharf O, Colevas AD. Adverse event reporting in publications compared with sponsor database for cancer clinical trials. *J Clin Oncol*. 2006;24:3933-8. [PMID: 16921045]
- Chan A-W, Hróbjartsson A, Jørgensen KJ, Gøtzsche PC, Altman DG. Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols. *BMJ*. 2008;337:a2299. [PMID: 19056791]
- Al-Marzouki S, Roberts I, Evans S, Marshall T. Selective reporting in clinical trials: analysis of trial protocols accepted by *The Lancet* [Letter]. *Lancet*. 2008;372:201. [PMID: 18640445]
- Hernández AV, Steyerberg EW, Taylor GS, Marmarou A, Habbema JD, Maas AI. Subgroup analysis and covariate adjustment in randomized clinical trials of traumatic brain injury: a systematic review. *Neurosurgery*. 2005;57:1244-53. [PMID: 16331173]
- Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, Chan A-W. Constraints on publication rights in industry-initiated clinical trials [Letter]. *JAMA*. 2006;295:1645-6. [PMID: 16609085]
- Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, Chan A-W. Ghost authorship in industry-initiated randomised trials. *PLoS Med*. 2007;4:e19. [PMID: 17227134]
- Lundh A, Krogsbøll LT, Gøtzsche PC. Access to data in industry-sponsored trials [Letter]. *Lancet*. 2011;378:1995-6. [PMID: 22153200]
- Hopewell S, Dutton S, Yu LM, Chan A-W, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ*. 2010;340:e723. [PMID: 20332510]
- Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.
- Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Med*. 2010;7:e1000217. [PMID: 20169112]
- Tetzlaff JM, Moher D, Chan A-W. Developing a guideline for clinical trial protocol content: Delphi consensus survey. *Trials*. 2012;13:176. [PMID: 23006145]
- World Medical Association. WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. Accessed at www.wma.net/en/30publications/10policies/b3/index.html on 1 October 2012.
- International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: General Considerations for Clinical Trials: E8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 17 July 1997. Accessed at www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf on 1 October 2012.
- International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials: E9. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 5 February 1998. Accessed at www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf on 1 October 2012.
- International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice: E6. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 10 June 1996. Accessed at www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf on 1 October 2012.
- Grimes DA, Hubacher D, Nanda K, Schulz KF, Moher D, Altman DG. The Good Clinical Practice guideline: a bronze standard for clinical research. *Lancet*. 2005;366:172-4. [PMID: 16005342]
- Sim I, Chan A-W, Gülmezoglu AM, Evans T, Pang T. Clinical trial registration: transparency is the watchword. *Lancet*. 2006;367:1631-3. [PMID: 16714166]
- Laine C, De Angelis C, Delamothe T, Drazen JM, Frizelle FA, Haug C, et al. Clinical trial registration: looking back and moving ahead [Editorial]. *Ann Intern Med*. 2007;147:275-7. [PMID: 17548404]
- Food and Drug Administration Amendments Act of 2007, HR 2580, 110th Congress, 1st Sess, Title VIII, §801 (2007). Expanded Clinical Trial Registry

Data Bank. Accessed at www.govtrack.us/congress/billtext.xpd?bill=h110-3580 on 1 October 2012.

42. **European Commission.** Communication from the Commission regarding the guideline on the data fields contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC to be included in the database on medicinal products provided for in Article 57 of Regulation (EC) No 726/2004 (2008/C 168/02). Official Journal of the European Union. 2008;51:3-4.

43. **Schulz KF, Altman DG, Moher D; CONSORT Group.** CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med.* 2010;152:726-32. [PMID: 20335313]

44. **National Research Council.** A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program. Washington, DC: National Academies Press; 2010.

45. **Chan A-W.** Out of sight but not out of mind: how to search for unpublished clinical trial evidence. *BMJ.* 2012;344:d8013. [PMID: 22214892]

46. **Wieseler B, Kerekes MF, Vervoelgyi V, McGauran N, Kaiser T.** Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports, and journal publications. *BMJ.* 2012;344:d8141. [PMID: 22214759]

47. **Reveiz L, Chan A-W, Krleža-Jerić K, Granados CE, Pinart M, Etxeandia I, et al.** Reporting of methodologic information on trial registries for quality assessment: a study of trial records retrieved from the WHO search portal. *PLoS One.* 2010;5:e12484. [PMID: 20824212]

48. **Dwan K, Altman DG, Cresswell L, Blundell M, Gamble CL, Williamson PR.** Comparison of protocols and registry entries to published reports for randomised controlled trials. *Cochrane Database Syst Rev.* 2011:MR000031. [PMID: 21249714]

49. **Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan A-W, Cronin E, et al.** Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One.* 2008;3:e3081. [PMID: 18769481]

50. **GlaxoSmithKline.** Public disclosure of clinical research. Global Public Policy Issues. October 2011. Accessed at www.gsk.com/policies/GSK-on-disclosure-of-clinical-trial-information.pdf on 1 October 2012.

51. **Turner L, Shamseer L, Altman DG, Schulz KF, Moher D.** Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. *Syst Rev.* 2012;1:60. [PMID: 23194585]

VISIT THE ANNALS BOOTH AT SUBSPECIALTY MEETINGS

Annals staff will be at these upcoming meetings:

American College of Cardiology, San Francisco, 9–13 March 2013

Digestive Disease Week, Orlando, 8–21 May 2013

American Thoracic Society, Philadelphia, 17–22 May 2013

American Society of Clinical Oncology, Chicago, 31 May–4 June 2013

American Diabetes Association, Chicago, 21–25 June 2013

Stop by the ACP/*Annals* booth and register to be a peer reviewer or discuss your thoughts for submissions or topic coverage with *Annals* staff.

Current Author Addresses: Dr. Chan: Women's College Research Institute, Women's College Hospital, University of Toronto, 790 Bay Street, Toronto, Ontario M5G 1N8, Canada.

Ms. Tetzlaff: Ottawa Methods Centre, Clinical Epidemiology Program, Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, Ontario K1H 8L6, Canada.

Dr. Altman: Centre for Statistics in Medicine, University of Oxford, Wolfson College Annexe, Linton Road, Oxford OX2 6UD, United Kingdom.

Dr. Laupacis: Keenan Research Centre at the Li Ka Shing Knowledge Institute of St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada.

Drs. Gøtzsche and Hróbjartsson: Nordic Cochrane Centre, Rigshospitalet Department 3343, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark.

Dr. Krleža-Jerić: Department of Epidemiology and Community Medicine, University of Ottawa, 451 Smyth Road, Ottawa, Ontario K1H 8M5, Canada.

Dr. Mann: Division of Medical Ethics and Humanities, University of Utah School of Medicine, 75 South 2000 East #108, Salt Lake City, UT 84132.

Dr. Dickersin: Center for Clinical Trials, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Mail Room W5010, Baltimore, MD 21205.

Dr. Berlin: Janssen Research & Development, Janssen Pharmaceutical Companies of Johnson & Johnson, 1125 Trenton Harborton Road, Titusville, NJ 08560.

Ms. Doré: UK Medical Research Council Clinical Trials Unit, 125 Kingsway, London WC2B 6NH, United Kingdom.

Dr. Parulekar: NCIC Clinical Trials Group, Cancer Research Institute, Queen's University, 10 Stuart Street, Kingston, Ontario K7L 3N6, Canada.

Dr. Summerskill: *The Lancet*, 32 Jamestown Road, London NW1 7BY, United Kingdom.

Dr. Groves: *BMJ*, BMA House, Tavistock Square, London WC1H 9JP, United Kingdom.

Dr. Schulz: Quantitative Sciences, FHI 360, Research Triangle Park, 2224 East NC Highway 54, Durham, NC 27713.

Dr. Sox: The Dartmouth Institute for Health Policy and Clinical Practice, The Geisel School of Medicine at Dartmouth, HB 7500, Hanover, NH 03755.

Dr. Rockhold: GlaxoSmithKline, 5 Moore Drive, PO Box 13398, Research Triangle Park, NC 27709.

Dr. Rennie: The Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, 3333 California Street, Laurel Heights 265, San Francisco, CA 94143-0936.

Dr. Moher: Clinical Epidemiology Program, Ottawa Hospital Research Institute, Department of Epidemiology and Community Medicine, University of Ottawa, 501 Smyth Road, Ottawa, Ontario K1H 8L6, Canada.

Author Contributions: Conception and design: A.-W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, P.C. Gøtzsche, K. Krleža-Jerić, A. Hróbjartsson, H. Mann, K. Dickersin, J.A. Berlin, W.R. Parulekar, K.F. Schulz, H.C. Sox, D. Rennie, D. Moher.

Analysis and interpretation of the data: A.-W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, P.C. Gøtzsche, K. Krleža-Jerić, A. Hróbjartsson, K. Dickersin, C.J. Doré, W.R. Parulekar, T. Groves, K.F. Schulz, F.W. Rockhold, D. Rennie, D. Moher.

Drafting of the article: A.-W. Chan, J.M. Tetzlaff, P.C. Gøtzsche, H. Mann, K. Dickersin, J.A. Berlin, C.J. Doré, W.R. Parulekar, K.F. Schulz.

Critical revision of the article for important intellectual content: A.-W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, K. Krleža-Jerić, A. Hróbjartsson, H. Mann, K. Dickersin, J.A. Berlin, C.J. Doré, W.R. Parulekar, W.S.M. Summerskill, T. Groves, K.F. Schulz, H.C. Sox, F.W. Rockhold, D. Rennie, D. Moher.

Final approval of the article: A.-W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, P.C. Gøtzsche, K. Krleža-Jerić, A. Hróbjartsson, H. Mann, K. Dickersin, J.A. Berlin, C.J. Doré, W.R. Parulekar, W.S.M. Summerskill, T. Groves, K.F. Schulz, H.C. Sox, F.W. Rockhold, D. Rennie, D. Moher.

Provision of study materials or patients: K. Krleža-Jerić, K. Dickersin. Statistical expertise: D.G. Altman, P.C. Gøtzsche, C.J. Doré, K.F. Schulz, F.W. Rockhold.

Obtaining of funding: A.-W. Chan, A. Laupacis, D. Moher.

Administrative, technical, or logistic support: A.-W. Chan, P.C. Gøtzsche, K. Krleža-Jerić.

Collection and assembly of data: A.-W. Chan, J.M. Tetzlaff, P.C. Gøtzsche, A. Hróbjartsson, K. Dickersin, C.J. Doré, W.R. Parulekar, K.F. Schulz.

Appendix Table. World Health Organization Trial Registration Data Set*

Item	Description
1. Primary registry and trial-identifying number	Name of primary registry and the unique identifier assigned by the primary registry
2. Date of registration in primary registry	Date when the trial was officially registered in the primary registry
3. Secondary identifying numbers	Other identifiers, if any Universal Trial Number Identifiers assigned by the sponsor Other trial registration numbers issued by other registries Identifiers issued by funding bodies, collaborative research groups, regulatory authorities, ethics committees/institutional review boards, etc.
4. Sources of monetary or material support	Major sources of monetary or material support for the trial (e.g., funding agency, foundation, company, institution)
5. Primary sponsor	Person, organization, group, or other legal entity that takes responsibility for initiating and managing a study
6. Secondary sponsor(s)	Additional persons, organizations, or other legal persons, if any, who have agreed with the primary sponsor to take on responsibilities of sponsorship
7. Contact for public queries	E-mail address, telephone number, and postal address of the contact who will respond to general queries, including information about current recruitment status
8. Contact for scientific queries	Name and title, e-mail address, telephone number, postal address, and affiliation of the principal investigator and e-mail address, telephone number, postal address, and affiliation of the contact for scientific queries about the trial (if applicable)
9. Public title	Title intended for the lay public in easily understood language
10. Scientific title	Scientific title of the study as it appears in the protocol submitted for funding and ethical review; include trial acronym, if available
11. Countries of recruitment	Countries from which participants will be recruited
12. Health condition(s) or problem(s) studied	Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error)
13. Intervention(s)	For each group of the trial, record a brief intervention name plus an intervention description Intervention name: For drugs, use the generic name; for other types of interventions, provide a brief descriptive name Intervention description: Must be sufficiently detailed for it to be possible to distinguish between the groups of a study; for example, interventions involving drugs may include dosage form, dosage, frequency, and duration
14. Key inclusion and exclusion criteria	Inclusion and exclusion criteria for participant selection, including age and sex
15. Study type	Method of allocation (randomized/nonrandomized) Blinding/masking (identify who is blinded) Assignment (e.g., single group, parallel, crossover, factorial) Purpose Phase (if applicable) For randomized trials: Method of sequence generation and allocation concealment
16. Date of first enrollment	Anticipated or actual date of enrollment of the first participant
17. Target sample size	Total number of participants to enroll
18. Recruitment status	Pending: Participants are not yet being recruited or enrolled at any site Recruiting Suspended: Temporary halt in recruitment and enrollment Complete: Participants are no longer being recruited or enrolled Other
19. Primary outcome(s)	The primary outcome should be the outcome used in sample size calculations or the main outcome used to determine the effects of the intervention For each primary outcome provide: Name of the outcome (do not use abbreviations) Metric or method of measurement used (be as specific as possible) Time point of primary interest
20. Key secondary outcome(s)	As for primary outcomes, for each secondary outcome provide: Name of the outcome (do not use abbreviations) Metric or method of measurement used (be as specific as possible) Time point of interest

* Adapted from www.who.int/ictrp/network/trds/en/index.html.